IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IDENIX PHARMACEUTICALS, INC., UNIVERSITA DEGLI STUDI DI CAGLIARI, CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE and L'UNIVERSITE MONTPELLIER II, Plaintiffs, v. GILEAD SCIENCES, INC. and GILEAD PHARMASSET LLC, Defendants.	C.A. No. 13-1987-LPS
IDENIX PHARMACEUTICALS, INC., UNIVERSITA DEGLI STUDI DI CAGLIARI, CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE and L'UNIVERSITE MONTPELLIER II, Plaintiffs, v. GILEAD PHARMASSET LLC, Defendant.	C.A. No. 14-109-LPS
IDENIX PHARMACEUTICALS, INC. and UNIVERSITA DEGLI STUDI DI CAGLIARI, Plaintiffs, v. GILEAD SCIENCES, INC. Defendant.	C.A. No. 14-846-LPS

DEFENDANTS' OPENING CLAIM CONSTRUCTION BRIEF

Dated: June 23, 2015

Douglas E. McCann (#3852)
Martina Tyreus Hufnal (4771)
Santosh V. Coutinho (#5470)
FISH & RICHARDSON P.C.
222 Delaware Avenue, 17th Floor
Wilmington, DE 19899
(302) 652-5070
dmccann@fr.com; hufnal@fr.com;
coutinho@fr.com

W. Chad Shear (#5711)
FISH & RICHARDSON P.C.
12390 El Camino Real
San Diego, CA 92130
(858) 678-5070
shear@fr.com

John M. Farrell
Rebecca Charnas Grant
FISH & RICHARDSON P.C.
500 Arguello Street, Suite 500
Redwood City, CA 94063
Telephone: (650) 839-5070
jfarrell@fr.com; rgrant@fr.com

Rebecca Shult
Tasha M. Francis
FISH & RICHARDSON P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, MN 55402
Telephone: (612) 335-5070
shult@fr.com; tfrancis@fr.com

Corrin N. Drakulich
FISH & RICHARDSON P.C.
1180 Peachtree St., N.E., 21st Floor
Atlanta, GA 30309
Telephone: (404) 892-5005
drakulich@fr.com

ATTORNEYS FOR DEFENDANTS GILEAD SCIENCES, INC. AND GILEAD PHARMASSET LLC

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page

Cases

TABLE OF AUTHORITIES

Page

The parties dispute the meanings of six terms: (1) nucleoside, (2) β-D-2′-methyl-ribofuranosyl nucleoside, (3) β-D-2′-C-branched pyrimidine nucleoside, (4) β-D-2′-C-branched pyrimidine ribonucleoside, (5) administering, and (6) leaving group. Gilead proposes constructions that are consistent with the plain meaning and intrinsic record, while Idenix offers litigation-inspired constructions that go well beyond the ordinary meaning and intrinsic support. Gilead therefore asks this Court to construe the asserted claims consistent with Gilead's proposed constructions.

I. NATURE AND STAGE OF THE PROCEEDINGS

Before the Court are three cases, two filed here, the other in the District Court for the District of Massachusetts. The Massachusetts action was transferred to this Court on June 30, 2014 and, because of the overlapping nature of the underlying subject matter, discovery for all three cases is being handled concurrently. Fact discovery is set to close on December 8, 2015. (D.I. 42, Scheduling Order, at 3.)[1] Opening expert reports are due on January 26, 2016, and rebuttal expert reports are due on March 8, 2016. Expert discovery is set to close on May 23, 2016. The claim construction briefing in this case is scheduled to continue through August 6, 2015. The Court has set a claim construction hearing for October 19, 2015. The first of the two scheduled trials is set to commence on October 11, 2016.

II. BACKGROUND

A. Hepatitis C and the Previous Standard of Care

[1] Unless otherwise specified, citations to docket item numbers refer to *Idenix Pharms. Inc., v. Gilead Sciences, Inc.*, No. 13-1987.

Hepatitis C (HCV)[2] is a viral disease that targets the liver. Since 2007, it has caused more deaths than HIV and AIDS. Over 170 million people worldwide, including more than 4 million in the US, suffer from HCV. ('054 patent at 1:22-23[3]; *see also* Declaration of Tasha M. Francis ("Francis Decl.") submitted concurrently herewith, Ex. 1 at 1576.) Left untreated, HCV ultimately leads to liver disease and is the primary cause of liver cancer and liver transplants. ('054 patent at 1:17-20.)

Because of the incredibly rapid rate at which HCV replicates in the body, as well as the large number of mutations that form during replication, developing an effective HCV therapy has been challenging. The traditional standard of care for HCV was a combination of antiviral medicines, taken for prolonged periods—up to 48 weeks—that caused side effects so severe that many patients were not eligible to take the treatment at all and others chose to live with the life-threatening disease rather than endure treatment. (*See id.* at 2:10-13, 3:4-6.) One of the prior medicines, interferon, is particularly debilitating, requiring weekly injections and causing side effects that run the gamut from cardiac abnormalities, persistent flu-like symptoms, and mental illnesses such as depression and anxiety. Moreover, the interferon-based treatment had a low rate of success in curing patients, so many patients endured the agony of treatment in vain.

Accordingly, dozens of pharmaceutical companies focused on developing new treatments for HCV that would allow doctors either to treat their patients without interferon at all or that significantly shortened the amount of time patients might have to take it. Failures abounded in this effort, by companies large and small, until Gilead's predecessor Pharmasset developed a

[2] To assist the court, attached as Exhibit A is a glossary of terms, abbreviations and acronyms used in the brief.

[3] U.S. Patent Nos. 6,914,054 ("the '054 Patent"), 7,608,597 ("the '597 Patent") and 7,608,600 ("the '600 Patent") were provided to the court previously as D.I. 9 at Ex. A and Ex. B and D.I. 1 at Ex. A, respectively.

game-changing drug, sofosbuvir.

On December 6, 2013, after expedited review, the FDA approved sofosbuvir as Gilead's Sovaldi®, a once-daily oral nucleotide analogue for the treatment of chronic HCV infection. The scientific and popular press around the world hailed the approval, which was prominently featured on the front pages of both the *New York Times* and the *Wall Street Journal*. (Francis Decl., Ex. 2 at A1; Ex. 3 at A1.) For the first time, many patients could now be cured of HCV without interferon, while others only needed to take interferon for 12 weeks. And, unlike the prior interferon-based treatment, most patients were cured. Just ten months later, Gilead took sofosbuvir to still another level when the FDA approved Harvoni®, which combines sofosbuvir with another drug to cure 95% of the patients who take it in as little as 8 weeks with no interferon. Sofosbuvir has revolutionized HCV treatment, replacing the horrible side effects that patients had to suffer for months on end with an uncertain prognosis with a single daily pill treatment that actually works.

B. The Science Behind Sofosbuvir

Sofosbuvir is a modified nucleotide analog. Nucleosides and nucleotides are fundamental building blocks of biological systems in RNA and DNA that generally consist of a sugar (circled in red) coupled to a base (circled in green). (See Figure 1.) A nucleo**s**ide with one, two or three phosphate groups (circled in blue) attached at what is called the 5′ position is known as a nucleo**t**ide.

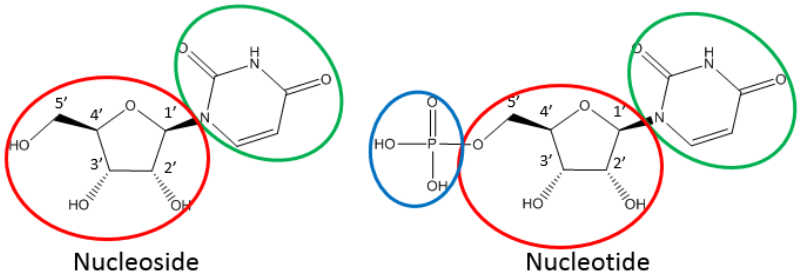

Figure 1. Chemical structures of a nucleoside and nucleotide.

Naturally-occurring nucleosides and nucleotides can be modified to incorporate different atoms or functional groups at various positions of the sugar and/or base. For example, sofosbuvir contains a fluorine (red) and a methyl group (blue) at the 2′ position of the sugar.

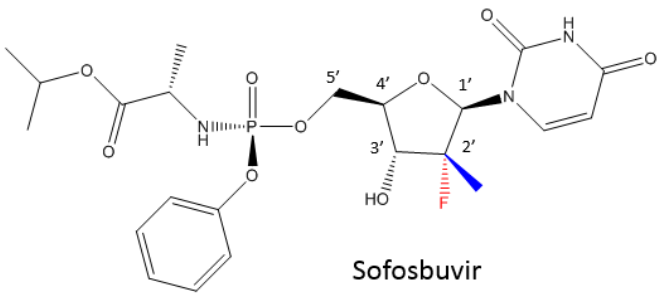

Figure 2. Chemical structure of sofosbuvir.

Some nucleosides and nucleotides cannot be directly administered to patients since they cannot be effectively absorbed from the gastrointestinal tract and successfully reach their intended target in the body. To be used as therapeutics, such nucleosides and nucleotides often have to be given as prodrugs to enhance their bioavailability. Prodrugs are compounds that undergo chemical conversion by metabolic processes in the body in order to ultimately deliver pharmacologically active drugs to the desired location. Sofosbuvir is a prodrug and undergoes metabolic conversion in the body to produce active compounds in the liver.

C. The Development of Sofosbuvir: Gilead's Groundbreaking HCV Treatment

As noted above, Gilead's predecessor, Pharmasset, invented sofosbuvir. This amazing invention dates back to work that began in the early 2000's. Pharmasset scientists experimented with a number of different nucleoside and nucleotide analogs including PSI-6130. (Figure 3).

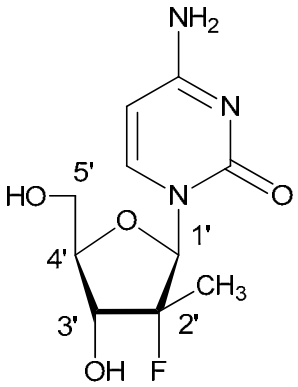

Figure 3. Chemical structure of PSI-6130.

PSI-6130, like sofosbuvir, has a methyl (CH_3) group and a fluorine (F)[4] at the 2′ position. Nucleoside compounds with both fluorine and methyl at the 2′ position had not been previously disclosed in the art, and there were no known methods for synthesizing such compounds. Despite the lack of teaching in the art, Pharmasset scientists synthesized PSI-6130 and found that it had excellent activity against HCV.

Pharmasset scientists continued their nucleoside work and eventually discovered sofosbuvir, which shares the 2′ fluoro (down) 2′ methyl (up) substitution pattern of PSI-6130. As noted above, sofosbuvir is a prodrug. (Francis Decl., Ex. 4 at § 12.4.) Only by delivering the compound as a prodrug can it efficiently treat HCV. (*See id*.)

D. The Plaintiffs and the Present Action

In the same timeframe of Pharmasset's development work, Idenix was also investigating different compounds for potential HCV treatments. Idenix's own lead anti-HCV candidate at

[4] Fluorine is also referred to as "fluoro" by skilled artisans.

that time, NM283 (also known as valopicitabine) was a 2′ methyl (up), 2′ hydroxyl (down) nucleotide prodrug. Like every other 2′ methyl, 2′ hydroxyl compound tested in clinic, NM283 was discontinued during phase II clinical trials due to toxicity. (*See* Francis Decl., Ex. 5 at 45; Ex. 6 at 453-454.) As such, Idenix's anti-HCV investigations never resulted in a successful treatment for HCV.

Now, in an effort to reap a windfall notwithstanding its years of failures, Idenix is trying to use the patent system to pretend that it, not Gilead, invented sofosbuvir, the compound that actually cured HCV, alleging in these actions that Sovaldi® (and, eventually, Harvoni®), infringe the '054, '597, and '600 Patents. And these actions are just the latest in a global dispute between Gilead and Idenix that spans across Canada, the United Kingdom, Australia, France, Germany, Norway, and both the European and United States Patent Offices. Every Court or Agency that has looked at the merits of the case has come out the exact same way—Idenix loses, and always for the exact same reason.

Simply put, Idenix's patent applications do not teach how to make critical features of the complicated nucleoside analogue that is at the core of Sovaldi®. And despite its allegation that one of skill could synthesize the compound based on the teachings of the prior art and its patents, Idenix itself failed for more than two years ***after*** the filing of its patent applications in numerous attempts to make it. (*See* Francis Decl., Ex. 7 at 19-21; *id.* at Ex. 8 at 23.)[5] Indeed, only after the publication of Gilead's patent application, which explained the proper synthetic method, was Idenix finally able to make the critical compound.

[5] The PTO declared certain asserted claims of the '600 patent invalid for failing to enable one of skill in the art. (Francis Decl., Ex. 9 at *2.) Idenix has appealed that decision. (Francis Decl., Ex. 10; Ex. 11.)

E. Plaintiffs' '054, '597 and '600 Patents

Three of Idenix's patents are at issue in this case—the '597, '054, and '600 patents. The '597 and '054 patents are related and share the same specification. They focus on the 2′ hydroxyl (down), 2′ methyl (up), compounds that Idenix was working on at the time. The specifications of these patents highlight that Idenix was not able to make a 2′ fluoro (down), 2′ methyl (up) compound and, therefore, did not disclose either the relevant structure or how to make it. In fact, of the 332 times that fluorine is mentioned in the patents, ***never*** is it shown in the 2′ down position. (Ex. B.)

The later-filed '600 patent, unlike the previous '054 and '597 patents, specifically claimed methods of treating HCV-infected hosts with 2′ fluorine (down) nucleoside analogs. But changing from a 2′ hydroxyl (down), 2′ methyl (up) to a 2′ fluoro (down), 2′ methyl (up), compound is not a simple matter. Atoms of a molecule cannot simply be swapped out like different colored Lego® bricks. The chemistry of synthesizing a new molecule is complex and highly unpredictable. And this is the reason that the USPTO, like the Courts in the UK and Norway, has already found that the '600 patent does not enable a person skilled in the art to actually synthesize a 2′ fluoro (down), 2′ methyl (up) compound and that Gilead, not Idenix, was the first to invent the compounds Idenix attempts to claim in these patents. (Francis Decl., Ex. 7 at 19-21; Ex. 8 at 40; Ex. 12 at 34; Ex. 13 at 2; Ex. 14 at GILEAD05080040-63.)

III. SUMMARY OF ARGUMENT

1. The term "nucleoside" in the '054 and '597 patents, "β-D-2′-methyl-ribofuranosyl nucleoside" in the '597 patent, and "β-D-2′-C-branched pyrimidine ribonucleoside" in the '054 patent are properly construed in accordance with their plain meanings, which all require specific functional groups at specific positions on the molecules. In an effort to create an infringement

case, Idenix attempts to impermissibly expand the scope of its claims through overbroad constructions of these phrases.

2. The "β-D-2′-C-branched pyrimidine nucleoside" and "β-D-2′-C-branched pyrimidine ribonucleoside" limitations in the '054 patent, as well as the "β-D-2′-methyl-ribofuranosyl nucleoside" limitation in the '597 patent, as properly construed, also exclude fluorine from the 2′ down position. Despite repeatedly referring to fluorine at other positions of the molecule, the specification consistently omits fluorine as an option at the 2′ down position. Idenix seeks to capture through claim construction that which it failed to describe and could not enable at the time of the invention—specifically a 2′ fluorine (down), 2′ methyl (up) nucleoside.

3. The terms "administering" in all three patents and "leaving group" in the '600 patent are also properly construed in accordance with their plain meaning. Idenix's constructions lack support in the specification and merely attempt to impermissibly expand the scope of the claims.

IV. ARGUMENT

A. Legal Standards for Claim Construction

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude," and, as such, claim construction must focus on the claim language itself. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation marks omitted). Claim terms "are generally given their ordinary and customary meaning" as understood by the skilled artisan at the time of the invention. *Id.* (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). "There are only two exceptions to this general rule: 1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee disavows the full scope of a claim term either in the

specification or during prosecution." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012).

Claim construction begins with the intrinsic evidence—namely, the claim language, the specification, and the prosecution history. *Phillips*, 415 F.3d at 1312–17. The claims provide important guidance both through "the context in which a term is used" and "differences among claims." *Id.* at 1314. The specification is "always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Id.* at 1315. The prosecution history may shed light on what a term means because it "inform[s] the meaning of the claim language by demonstrating how the inventor understood the invention." *Philips,* 415 F.3d at 1317. Extrinsic evidence may also be considered to assist the court in determining the meaning of particular terminology to those of skill in the art. *Id.* at 1317–19.

The construction "that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end the correct construction." *Id.* at 1316.

B. The '054 and '597 Patents: "Nucleoside"

Disputed Term	Gilead's Proposal	Idenix's Proposal
Nucleoside (Asserted Claims 25 and 27 of the '054 patent and claims 1, 2, 4-13, 16, 17, 19, 23, 28, 30, and 31 of the '597 patent)	A compound comprising base and sugar moieties, with a hydroxyl group at the 5′ position.	A compound comprising a base linked to a sugar.

Gilead's proposed construction of "nucleoside" is simply the term's plain and ordinary meaning to a person skilled in the art. This ordinary meaning is relied upon by those skilled in the art to distinguish between nucleo**s**ides and nucleo**t**ides and is consistent with the intrinsic record, including the specification, and with the definitions that Idenix has used for this term in worldwide proceedings. Idenix's proposed construction, on the other hand, is broader than the

ordinary meaning and is part of a litigation-driven strategy to read the claims to cover compounds that they were never intended to cover and that Idenix did not invent.

"Nucleoside" has a plain and ordinary meaning that is readily apparent to those in the art—a compound comprising base and sugar moieties, with a hydroxyl group at the 5′ position. (See Figure 1; *see also* Declaration of Jason Micklefield, Ph.D. ("Micklefield Decl.") submitted concurrently herewith at ¶¶ 22-26, 45-53.) Indeed, the very difference between a nucleoside and a nucleotide is the functional group that appears at the 5′ position. (Micklefield Decl. at ¶¶ 22-26, 45-53.) A nucleoside has an "OH" group at the 5′ position. (Micklefield Decl. at ¶¶ 24, 47-53.) In contrast, a nucleotide has a phosphate at the 5′ position.

The very structure of Idenix's patent claims evidences this understanding in the art. When Idenix wants its claims to cover ***nucleosides***, it says so. By contrast, when it wants it claims to cover ***nucleotides*** as well as ***nucleosides***, it writes claims that allow for "nucleosides and phosphates thereof," allowing those claims to cover more than just a hydroxyl group at the 5′ position. For example, claims 1, 2, 4, 8, 11, 12, 13, 28, 30 and 31 of the '597 patent recite a nucleoside "or a phosphate thereof." Different terms used in separate claims are generally assumed to have different meanings, *see Seachange Int'l, Inc. v. C-COR, Inc.,* 413 F.3d 1361, 1368 (Fed. Cir. 2005), but, under Idenix's proposed construction of "nucleoside," that term would cover the very same thing as a "nucleoside or a phosphate thereof." That cannot be correct—it would render the "or a phosphate thereof" language in the '597 claims entirely superfluous, because a nucleoside would be permitted to have any functional group, including a phosphate, at the 5′ position. Because claims must be "interpreted with an eye toward giving effect to all terms in the claim," Idenix's proposed construction is simply wrong. *See Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006); *see also Elekta Instrument S.A. v. O.U.R.*

Scientific Int'l, Inc., 214 F.3d 1302, 1305–07 (Fed. Cir. 2000) (refusing to adopt a claim construction which would render claim language superfluous).

Gilead's proposed construction of nucleoside, on the other hand, is consistent with the specifications of the '054 and '597 patents (which are identical). For example, Figure 1 of the '054 and '597 patents, entitled "Chemical Structure of Illustrative Nucleosides," presents the structures of ten "illustrative nucleosides," ***all*** of which contain hydroxyl groups at the 5′ position. ('054 patent at Figure 1.) Additionally, in discussing other substituents that can be incorporated into the nucleosides of the invention, the specifications recognize that the 5′ position contains a hydroxyl group, explaining that certain substituents can be "incorporated into the nucleoside, ***preferably at the 5′-OH position of the nucleoside***." ('054 patent at 40:5-25; '597 patent at 40:7-26 (emphasis added).)

Moreover, independent claims 1-9 and 22-24 of the '054 patent all recite "[a] method for treatment of a Hepatitis C virus infection in a human in need thereof, comprising administering to said human an antivirally effective amount of a β-D nucleoside compound of the structure…" followed by drawings of nucleosides. Each of the twelve nucleosides depicted in independent claims 1-9 and 22-24 contain a hydroxyl group at the 5′ position of the sugar. (*See* Micklefield Decl., Figure 17 at 19.) Thus, when looking at the plain meaning of the claims, a person of ordinary skill in the art would have understood the term "nucleoside" to refer to a compound comprising base and sugar moieties, with a hydroxyl group at the 5′ position.

Furthermore, like the literature in the art, the specifications plainly distinguish a nucleoside from a nucleotide in a manner entirely consistent with the way those terms are used by persons skilled in the art. (*See, e.g.*, '054 patent at 39:34-37 ("Any of the nucleo**s**ides described herein can be administered as a nucleo**t**ide prodrug to increase the activity,

bioavailability, stability or otherwise alter the properties of the nucleoside." (emphasis added).) Gilead's construction is consistent with this usage, but Idenix's construction is not. (Micklefield Decl. at ¶¶ 54-58.) The Court should adopt Gilead's construction.

Gilead's proposed construction is also consistent with dictionary and textbook definitions of the term. *See Baran v. Med. Device Tech., Inc.*, 616 F.3d 1309, 1316 (Fed. Cir. 2010) (approving the district court's reliance on "several dictionary definitions" to construe a term to "comport[] with [its] plain meaning"); *see also Phillips*, 415 F.3d at 1314. Persons of skill in the art understand that a "nucleoside," which contains a hydroxyl (-OH) group at the 5′ position, is distinct from a "nucleotide," which contains a mono-, di- or tri-phosphate at the 5′ position. (*See* Micklefield Decl., Ex. C at 107.) The figure below, in which the 5′ hydroxyl groups are squared in blue and the mono-phosphate groups are circled in red, illustrates this distinction:

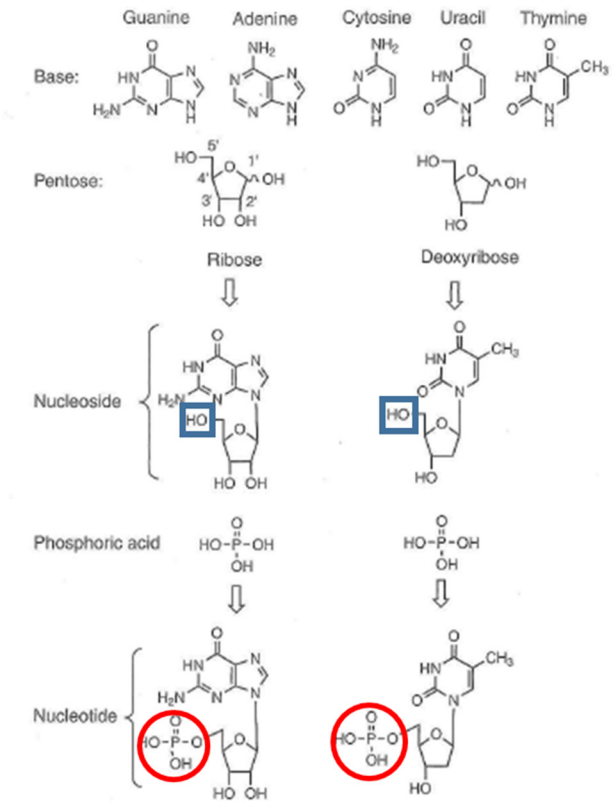

FIGURE 16-1. Structures of components of nucleotides.

Figure 4. Chemical structures of representative nucleosides and nucleotides (Micklefield Decl., Ex. C at 107).

And this textbook definition is consistent with what Idenix has agreed, in other proceedings, is the plain and ordinary meaning of nucleoside, namely, that a nucleoside requires a hydroxyl group at the 5′ position. (*See, e.g.*, Francis Decl., Ex. 15 at 2.)

Now, however, Idenix wishes to eliminate that requirement from the claims, likely because it recognizes that, under the proper construction requiring the 5′ hydroxyl, Gilead's sofosbuvir compound (which does ***not*** have a 5′ hydroxyl), cannot infringe the claims of the '054 patent. Idenix should not be allowed to improperly expand the scope of its claims through claim construction.

C. The '597 Patent: "β-D-2′-methyl ribofuranosyl nucleoside"

Disputed Term	Gilead's Proposal	Idenix's Proposal
β-D-2′-methyl ribofuranosyl nucleoside (Asserted Claims 1, 2, 4-13, 16, 17, 19, 23, 28, 30, 31)	A β-D-nucleoside that includes a five member sugar ring with a methyl group in the 2′ up position and hydroxyl groups at the 2′ down and 3′ down positions. [To the extent the term is not construed to require a hydroxyl group at the 2′ down position, the construction should specify that there is no fluorine in the 2′ down position.]	A β-D-nucleoside that includes a five member sugar ring with a methyl group in the 2′ up position and non-hydrogen substituents at the 2′ down and 3′ down positions

The parties agree on the general structure required for a β-D-2′-methyl ribofuranosyl nucleoside. The only dispute on this term concerns the substituents at the 2′ and 3′ down positions on the nucleoside's sugar ring. Gilead's proposed construction, consistent with the plain and ordinary meaning of a "ribofuranosyl nucleoside," requires that there be hydroxyl groups at the 2′ and 3′ down positions on the sugar ring. Idenix, again advancing a litigation-

driven position to broaden its claims beyond the ordinary meaning, proposes a construction requiring only that the 2′ and 3′ positions contain non-hydrogen substituents.

The plain and ordinary meaning of "β-D-2′-methyl ribofuranosyl nucleoside" is a compound consisting of a base coupled to ***ribofuranose*** in β-D configuration with at methyl at the 2′ (up) position. (*See e.g.*, Micklefield Decl., Ex. G at 136; *see also* Micklefield Decl. at ¶¶ 59-68.)

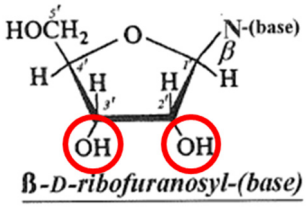

Figure 5. Structure of β-D-ribofuranosyl nucleoside. (Micklefield Decl., Ex. G at 136.)

Ribofuranose, depicted below, is a five member ribose sugar with the molecular formula $C_5H_{10}O_5$ that contains hydroxyl groups at the 2′ (down) and 3′ (down) positions. (*See id.*; Francis Decl., Ex. 16 at 574; Ex. 17 at 8289; *see also* Micklefield Decl., Ex. F at 227.)

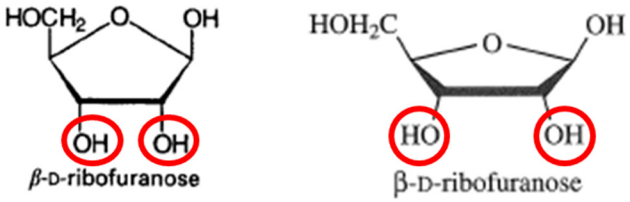

Figure 6. Structure of β-D-ribofuranose. (Francis Decl., Ex. 16 at 574; Micklefield Decl., Ex. F at 227.)

A person skilled in the art would have understood the inclusion of the term "ribofuranosyl" in the '597 claims to require the 2′ and 3′ (down) hydroxyl groups that are present in ribofuranose. (Micklefield Decl. at ¶¶ 60-71.)

Idenix clearly understood this plain and ordinary meaning when it explained to the Patent Office exactly what the structure of "β-D-2′-methyl ribofuranosyl nucleoside" was. In a Response to Office Action dated March 10, 2006, Idenix stated that "[s]upport for the pending claims can be found throughout provisional application 60/206,585…Specifically, the compound with ***formula VI*** on page 23 discloses a ***β-D-2′-methyl ribofuranosyl nucleoside***, wherein base is a purine or pyrimidine base, R^4 may be alkyl, and R may be H." (Micklefield Decl., Ex. H at 5 (emphasis added).) As shown below, Formula VI depicts a base coupled to a sugar containing hydroxyl groups at the 2′ down and 3′ down positions. (Micklefield Decl., Ex. I at 23.)

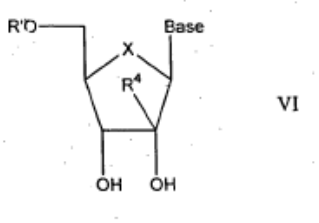

Figure 7. Formula VI from Applicants' Remarks Dated March 10, 2006.

It is only now, when Idenix needs a broader construction to salvage its infringement theory that it pushes for a construction well beyond the plain and ordinary meaning and different than it explained to the Patent Office. Indeed, Idenix's proposed construction, which requires only non-hydrogen substituents at the 2′ and 3′ down positions, would essentially read the "ribofuranosyl" requirement out the claim entirely.

The Court should adopt Gilead's proposed construction of β-D-2′-methyl ribofuranosyl nucleoside, which aligns with the plain and ordinary meaning and is supported by Idenix's statements in prosecution and internal documents.[6]

[6] To the extent that the Court does not adopt Gilead's construction requiring a hydroxyl group at the 2′ down position, the construction of β-D-2′-methyl ribofuranosyl nucleoside should still

D. The '054 Patent: "β-D-2′-C-branched pyrimidine nucleoside"

Disputed Term	Gilead's Proposal	Idenix's Proposal
β-D-2′-C-branched pyrimidine nucleoside (Asserted Claims 25, 27 of the '054 patent)	A β-D pyrimidine nucleoside with two non-hydrogen substituents at the 2′ position, at least one of which is connected at the 2′ position through a carbon-to-carbon bond, and no fluorine at the 2′ down position.	A β-D pyrimidine nucleoside having two non-hydrogen substituents at the 2′ position, at least one of which is connected at the 2′ position through a carbon-to-carbon bond

The parties agree that the term "β-D-2′-C-branched pyrimidine nucleoside" refers to a "β-D pyrimidine nucleoside with two non-hydrogen substituents at the 2′ position, at least one of which is connected at the 2′ position through a carbon-to-carbon bond." The parties' dispute over the term concerns whether fluorine is a possible substituent at the 2′ down position. Properly construed, fluorine is excluded as a 2′ substituent.

Although the ordinary meaning of the term "2′-C-branched" may not specify particular allowed substituents for the 2′ position, the term must be read in the context in which it is used rather than viewed in a vacuum. *Philips*, 415 F.3d at 1313 (*citing Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005)) ("We cannot look at the ordinary meaning of the term . . . in a vacuum. Rather, we must look at the ordinary meaning in the context of the written description and the prosecution history.") And, based on Idenix's specification, it could not be more clear—fluorine is not allowed as a possible substituent at the 2′ down position. Every single time that the specification discusses possible substituents for the 2′ down position, it does not include fluorine in the list, even though it lists other halogen atoms, including bromine, iodine, and chlorine. (*See* '054 patent, 43:53-44:26; 47:5-43; 50:39-51:13.) For example, col. 47 of the '054 patent provides a description of the "General Synthesis of 2′-C-branched

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specify that fluorine is excluded from the 2′ (down) position for the reasons discussed below in Section D.

nucleosides." At the 2′ down position, also referred to as R^7, the patent recites various substituents: hydrogen, OR_2, hydroxyl, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, --C(O)O(alkyl), --(C(O)O(lower alkyl), --O(acyl), --O(lower acyl), --O(alkyl), --O(lower alkyl), --O(alkenyl), ***chlorine, bromine, iodine***, NO_2, NH_2, --NH(lower alkyl), --NH(acyl), --N(lower alkyl)$_2$, --N(acyl)$_2$." ('054 patent at 47:17-23 (emphasis added).) Despite the fact that this list includes millions of possible substituents at 2′ down position, including three other halogens, fluorine is markedly absent.

In total, fluorine is mentioned 332 times in the specification of the '054 and '597 patents, ***never*** once at the 2′ down position. (*See* Ex. B (Table of "Fluoro" cites in patent specification).) Its exclusion from the 2′ down position makes sense because Idenix ***did not invent*** and, indeed, could not make 2′ fluorine (down), 2′ methyl (up) compounds. (Francis Decl., Ex. 7 at 19-21; Ex. 13 at 2; Ex. 8 at 40; Ex. 14 at GILEAD05080040-63; Ex. 12 at 34.) Gilead's proposed construction excluding fluorine at the 2′ down position "most naturally aligns with the patent's description of the invention," *Phillips*, 415 F.3d at 1316, whereas Idenix's litigation-driven approach seeks to impermissibly expand the scope of the claims.

Indeed, the specification's glaring omission of fluorine as a 2′ down substituent, while repeatedly including fluorine as a possible substituent at other positions on the sugar ring, is sufficient to define the "2′-C- branched" term in the claims to exclude 2′ down fluorine. The Federal Circuit has held that "[e]ven when guidance is not provided in explicit definitional format, the specification may define claim terms by implication such that the meaning may be found in or ascertained by a reading of the patent documents." *In re Abbott Diabetes Care Inc.,* 696 F.3d 1142, 1150 (Fed. Cir. 2012) citing *Irdeto Access, Inc., v. Echostar Satellite Corp.,* 383 F.3d 1295, 1300 (Fed. Cir. 2004) (internal quotations omitted). The Court explained that

"[w]hen a patentee uses a claim term throughout the entire patent specification, in a manner consistent with only a single meaning, he has defined that term 'by implication.'" *Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1271 (Fed. Cir. 2001) (internal citations omitted). The Federal Circuit recognizes "there is sometimes 'a fine line between reading a claim in light of the specification, and reading a limitation into the claim from the specification'" but concludes an Applicant manifests a clear intent to limit a term when it "repeatedly, consistently, and exclusively" use a term in a particular context throughout the specification. *Irdeto Access, Inc. v. Echostar Satellite Corp.*, 383 F.3d 1295, 1303 (Fed. Cir. 2004). Idenix has done just that here.

The absence of fluorine at the 2′ down position is not an oversight, as made clear from reading the remainder of the specification. Despite not listing fluorine as a possible 2′ down substituent, Idenix listed fluoro in the definition of functional groups at 2′ **up** position. (*See* '054 patent at 47:40-41 ("R^6 is an alkyl, chloro-, bromo-, ***fluoro***-, iodo-alkyl (i.e. CF_3), alkenyl, or alkynyl (i.e., allyl)") (emphasis added).) Furthermore, throughout the rest of the specification, Idenix used the term "fluoro" 332 times but never once to describe fluorine at the 2′ down position in 2′-C-branched nucleosides. (Ex. B.) Rather, every embodiment disclosed in the specification excludes fluorine at the 2′ down position. The fact that the patent discusses fluorine extensively elsewhere, but chooses not to list it as a possible 2′ down substituent for any compound, including this specific claimed compound, provides notice to a person skilled in the art that 2′ down fluorine is not intended to be included as part of the invention. *Pi-Net Int'l Inc. v. JPMorgan Chase & Co.*, 42 F. Supp. 3d 579, 588-89 (D. Del. 2014) ("The claims and specification of a patent serve an important public notice function, apprising others of what is available to them."); *see also Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1249

(Fed. Cir. 2008); *see also* (Micklefield Decl. ¶¶ 78-81.) The patent claims should be interpreted in a manner that is consistent with the specification so that a person skilled in the art can understand their scope.

An examination of the facts surrounding Idenix's development of the invention also demonstrates that the exclusion of fluorine from the 2′ down position of nucleosides claimed in both the '054 patent and '597 patent was intentional. 2′ fluorine down compounds were simply not part of what Idenix invented. Fact-finding bodies in the U.S. and abroad have determined that Idenix was not able to successfully synthesize 2′-branched nucleosides containing fluorine at the 2′ down position until after publication of Pharmasset's patent application, which contains specific step-wise examples for preparing such compounds. (*See* Francis Decl., Ex. 8 at 15; Ex. 18 at 22; Ex. 7 at 19-21.) Idenix impermissibly seeks to capture through claim construction that which it did not describe and could not even make (and therefore did not claim) at the time of the patents—specifically 2′ fluoro (down), 2′ methyl (up) nucleosides. The Court should reject Idenix's litigation-driven construction and adopt Gilead's construction that excludes fluorine from the 2′ down position, consistent with Idenix's specification describing the compounds that are intended to be part of the invention. *See, e.g.*, *Wang Labs., Inc., v. Am. Online, Inc.,* 197 F.3d 1377, 1383 (Fed. Cir. 1999) (affirming construction of term "frame" to be limited to character-based protocols and exclude bit-mapped protocols, because the only system described and enabled in the specification used a character-based protocol and evidence showed that the patentee had been unable to develop a bit-mapped protocol.)

E. The '054 Patent: "β-D-2′-C-branched pyrimidine ribonucleoside"

Disputed Term	Gilead's Proposal	Idenix's Proposal
β-D-2′-C-branched pyrimidine ribonucleoside	A β-D pyrimidine nucleoside with a non-hydrogen substituent at the 2′ up position that is connected at the 2′ position	A β-D pyrimidine ribonucleoside having a non-hydrogen substituent at the 3′

(Asserted Claims 26-27 of the '054 patent)	through a carbon-to-carbon bond, and hydroxyl groups at the 2′ down and 3′ down positions. [To the extent the term is not construed to require a hydroxyl group at the 2′ down position, the construction should specify that there is no fluorine in the 2′ down position.]	down position and two non-hydrogen substituents at the 2′ position, at least one of which is connected at the 2′ position through a carbon-to-carbon bond

The parties agree that the terms "β-D pyrimidine nucleoside" and "β-D-2′-C-branched pyrimidine ribonucleoside" differ only in that the latter is limited to a ribonucleoside rather than a nucleoside in general. The parties' only dispute is whether a ribonucleoside requires hydroxyl groups at the 2′ and 3′ down positions or whether the 2′ and 3′ positions can contain any non-hydrogen substituent. Gilead's construction, which requires the 2′ and 3′ down hydroxyl groups that are present in a ribose sugar, is consistent with the plain and ordinary meaning and the intrinsic record, while Idenix's improper construction effectively reads out the "ribo" limitation.

A "β-D-pyrimidine ribonucleoside" is simply a nucleoside containing a ribose sugar coupled to a pyrimidine base in the β-D configuration. (*See* Micklefield Decl., Ex. M at 1571; *see also* Micklefield Decl. at ¶¶ 82-89.) Like the ribofuranose compound discussed in Section C, a ribose sugar contains hydroxyl groups at the 2′ and 3′ down positions. (*See* Francis Decl., Ex. 16 at 574; Ex. 19 at 30.) Because a ribose sugar by definition contains a hydroxyl group at the 2′ down position, fluorine cannot be present at the 2′ down position as only one substituent can be at the 2′ down position. Idenix's construction, which allows for any two non-hydrogen substituents at the 2′ position, and does not require a hydroxyl group at 2′ down or 3′ down, effectively ignores the requirement, apparent from the plain language of the claim, that the sugar be a ribose sugar.

The specification of the '054 patent supports Gilead's proposed construction. For example, the patent states "[i]n a particular embodiment, the 2′-C-branched ribonucleoside is

desired. The synthesis of a ribonucleoside is shown in Scheme 3." ('054 patent at 48:24-26). Scheme 3 depicts the synthesis of a 2′-C′-branched ribonucleoside which contains hydroxyl groups at the 2′ down and 3′ down positions. ('054 patent, Scheme 3; *see also* Micklefield Decl. at ¶¶ 91-92).

The Court should adopt Gilead's proposed construction of "β-D-2′-C-branched ribonucleoside" because it is consistent with the plain meaning and specification. (Micklefield Decl. at ¶ 93.) To the extent that the Court does not adopt Gilead's construction requiring a hydroxyl group at the 2′ down position, the construction should still specify that fluorine is excluded from the 2′ down position for the reasons discussed above in Section D. Idenix's specification makes plain that fluorine is not one of the substituents that is contemplated at the 2′ down position. Thus, to remain true to the scope of Idenix's actual invention, any construction of the phrase "β-D-2′-C-branched ribonucleoside" must exclude fluorine at 2′ down.

F. The '054, '597 and '600 Patents: "administering"

Disputed Term	Gilead's Proposal	Idenix's Proposal
Administering (Asserted Claims 25-27 of the '054 patent, 1, 2, 4-14, 16, 17, 19, 23, 28 and 29 of the '597 patent, and 1-9, 12, 20, 50-57, 64 and 76-83 of the '600 patent)	Providing externally. A metabolite of an administered compound that is created by in vivo transformation is not administered.	Making available

Gilead's construction of "administering"—providing externally—reflects the plain and ordinary meaning of the term in the art. The usage of the term in the '054, '597, and '600 patents is consistent with that ordinary meaning. Idenix's proposed construction, on the other hand, is contrary to the ordinary meaning of the term and has no support in the intrinsic record.

In the context of pharmaceutical products, "administering" refers to providing a drug to a

patient in any of a variety of ways, for example, orally, intravenously, topically, or by another route. "Administering" the drug ends once the patient takes the drug; it does not include metabolism of the drug once it is already in the body. (Micklefield Decl. at ¶¶ 94-96.) Dictionary definitions confirm this ordinary meaning. For example, the American Heritage Dictionary defines "administer" as "to apply as a remedy" and "to mete out; dispense," words associated with ***externally provided*** compounds, not metabolites formed in vivo. (*See* Micklefield Decl., Ex. N at 22.) The case law also supports this ordinary meaning. In *Hoffmann-La Roche Inc. v. Apotex Inc.*, No. CIV.A.07-4417SRCMAS, 2010 WL 1875569, at *8 (D.N.J. May 10, 2010), the court explained that "administering stops when the giving stops, and the giving stops as soon as the patient has received the medication. Does the giver continue to give while the medication gets digested and travels through the bloodstream? This Court thinks not." *See also Schering Corp. v. Glenmark Pharm. Inc*., USA, No. CIV A 07-1334 (JLL), 2008 WL 4307189, at *8 (D.N.J. Sept. 16, 2008) (finding that one of ordinary skill in the art for a method of treatment claim would understand that "metabolites form only *after* a drug is 'administered,' i.e., ingested").

The specifications of Idenix's patents are fully consistent with this ordinary meaning, repeatedly using the term "administering" to refer to providing the drug externally, and not in a way that encompasses metabolites formed by *in vivo* transformation. For example, the patents distinguish between the drug that is administered and what is formed ***after*** administration, noting that "[t]he active compound can be administered as any salt or prodrug that ***upon administration to the recipient*** is capable of providing directly or indirectly the parent compound, or that exhibits activity itself." ('054 patent at 36:53-56 (emphasis added); '600 patent at 110:2-5 (emphasis added); *see also* '054 patent at 38:58-63; '600 patent at 109:44-49.)

And the patents repeatedly use "administering" to refer to the point at which a patient takes a drug, not to what happens to that drug in the body once the patient has already taken it. For example, the patents refer to "the professional judgment of the person ***administering*** or supervising the administration of the compositions." (*See, e.g.,* '054 patent at 13:61-67; '600 patent at 38:43-48.) They also discuss the dosage forms in which the drug is administered, i.e., provided externally to a patient, explaining that the compositions of the invention are "conveniently ***administered*** in unit any [sic] suitable dosage form, including but not limited to one containing 7 to 3000 mg, preferably 70 to 1400 mg of active ingredient per unit dosage form." (*See, e.g.,* '054 patent at 42:9-12; '600 patent at 116:63-66.) And these dosage units "can be ***administered*** by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form." (*See, e.g.,* '054 patent at 41:62-65; '600 patent at 116:45-47.) Specifically, "[f]or the purpose of oral therapeutic ***administration***, the active compound[s] can be incorporated with excipients and used in the form of tablets, troches, or capsules." (*See, e.g.,* '054 patent at 42:39-42; '600 patent at 117:31-34.) None of these disclosures can possibly include "administering" a metabolite that forms in vivo. Metabolites formed in vivo cannot be administered by professionals in dosage units "orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form" or packaged into tablets. (*See* Micklefield Decl. at ¶¶ 97-99.)

In a case with similar facts, another court in this circuit held that "administering" referred only to giving a compound to a patient externally:

> The patent specification does not expressly define "administered," but . . . defines the term by implication. "Administering" is used primarily in conjunction with the term "dose" or "dosage" throughout the specification. Such use suggests that "administered" applies only to those compounds given to a patient externally, not those that contemplate the in vivo formation of metabolites with respect to the recited compounds.

Schering, 2008 WL 4307189, at *4; *see also Schering Corp. v. Mylan Pharm., Inc.*, No. CIV.A. 09-6383 JLL, 2011 WL 2446563, at *7-*8 (D.N.J. June 15, 2011).[7]

Because the Idenix patents repeatedly use the term "administering" consistent with its ordinary meaning of the external providing of compounds and because the patents do not offer any contrary or broader definition, the court should construe the term as "providing externally."

G. The '600 Patent: "leaving group"

Disputed Term	Gilead's Proposal	Idenix's Proposal
leaving group (Asserted Claims 1-9, 12, 20, 50-57, 64 and 76-83 of the'600 patent)	An atom or group of atoms that is cleaved in its entirety from the administered compound.	A moiety that includes one or more atoms that are cleaved, i.e., a prodrug moiety

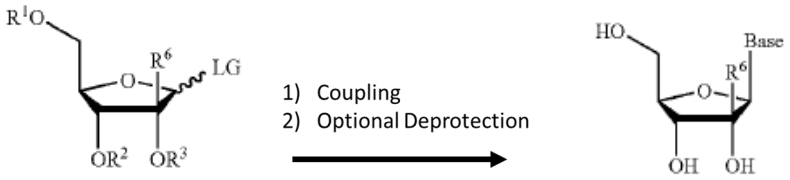
Once again, on the term "leaving group," Gilead has proposed a construction that is consistent with the term's plain and ordinary meaning and the intrinsic record, while Idenix has proposed a construction that attempts to broaden the ordinary meaning in hopes of making the claim read on Gilead's sofosbuvir products.

Gilead's construction of "leaving group" is based on the plain and ordinary meaning. By both common sense and understanding in the art, a ***leaving group*** is the group that ***leaves*** in a chemical reaction when displaced by the addition of a new group; it does not partially stay. (Francis Decl., Ex. 21 at 308 ("The leaving group is whatever leaves with its electrons, the entirety of it."); Ex. 22 at G-15 (defining leaving group as "a group displaced from a reactant in a

[7] This case is distinguishable from the recent claim construction decision in *Gilead Sciences, Inc. v. Merck & Co.*, 5:13-cv-04057-BLF (N.D. Cal. May 1, 2015), where the court construed "administering" as "providing a compound of the invention or a prodrug of a compound of the invention to patient in need." The patent at issue in that case, unlike the patents here, defined "administering" in the specification to include prodrug use. Moreover, the construction that Idenix seeks here is not the same as the construction adopted in that case.

substitution or elimination reaction.”))

The specification of the ’600 patent fully supports this ordinary meaning. For instance, in the context of describing a route for coupling a base to a sugar, the patent discusses a sugar with a “leaving group (LG), for example an acyl group or a halogen,” which, after certain modifications to the sugar, “can then be coupled to the BASE.” (’600 patent at 121:39-42, 122:30-33). An example of such a reaction is shown in “scheme 3,” which depicts a leaving group (LG) ***leaving in its entirety*** and being replaced with a Base:



(’600 patent at 122:53-123:5; *see also id.* at 125:25-28, 126:39-67). By contrast, the specification does not contain any examples where a group that does not leave in its entirety is referred to as a leaving group.

The Court should therefore adopt Gilead’s proposed construction of a leaving group as “an atom or group of atoms that is cleaved ***in its entirety*** from the administered compound.”

V. CONCLUSION

For the foregoing reasons, and those to be stated in later briefing and at argument, Gilead respectfully requests that the Court adopt its proposed constructions.

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FISH & RICHARDSON P.C.

By: */s/ Martina Tyreus Hufnal*

Douglas E. McCann (#3852)
Martina Tyreus Hufnal (4771)
Santosh V. Coutinho (#5470)
222 Delaware Avenue, 17th Floor
Wilmington, DE 19899
(302) 652-5070
dmccann@fr.com; hufnal@fr.com;
coutinho@fr.com

W. Chad Shear (#5711)
FISH & RICHARDSON P.C.
12390 El Camino Real
San Diego, CA 92130
(858) 678-5070
shear@fr.com

John M. Farrell
Rebecca Charnas Grant
FISH & RICHARDSON P.C.
500 Arguello Street, Suite 500
Redwood City, CA 94063
Telephone: (650) 839-5070
jfarrell@fr.com; rgrant@fr.com

Rebecca Shult
Tasha M. Francis
FISH & RICHARDSON P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, MN 55402
Telephone: (612) 335-5070
shult@fr.com; tfrancis@fr.com

Corrin N. Drakulich
FISH & RICHARDSON P.C.
1180 Peachtree St., N.E., 21st Floor
Atlanta, GA 30309
Telephone: (404) 892-5005
drakulich@fr.com

ATTORNEYS FOR DEFENDANTS GILEAD SCIENCES, INC. AND GILEAD PHARMASSET LLC